

**REMARKS**

This Supplemental Preliminary Amendment is being filed to correct two, small and inadvertant errors introduced with the Preliminary Amendment filed May 6, 2002. The length and apparent complexity of this document is due solely to the required protocol for making amendments and not to any length or complexity of the amendments made.

In the Remarks portion of the May 6, 2002 Preliminary Amendment (at page 64 thereof), it was pointed out that the specification description contained an error with respect to the definition of certain of the rings. Specifically, it was noted that these rings were intended to be described as being 4-6 membered saturated heterocyclic rings instead of 5-6 membered saturated heterocyclic rings, for the reasons and with the support there described. Accordingly, a number of specification amendments were presented to make this correction. However, an error in the correction made at specification page 48 was recently noted, and it was further noted that this same error had been carried into new claim 39 presented in the Preliminary Amendment.

The purpose of this Supplemental Preliminary Amendment is to correct this ring definition at specification page 48 and in claim 39, and to make it consistent with the remainder of the specification and claims. Specifically:

- At page 48 of the specification, line14, R<sup>5a</sup> was originally defined as “a 5- or 6-membered saturated heterocyclic group . . .” By the Preliminary Amendment of May 6, 2002, this was changed to read “a 4- or 6-membered saturated heterocyclic group . . .” However, as explained in the Remarks portion of the Preliminary Amendment, the intent was to have the definition refer to a 4-6 membered ring, and therefore the present specification

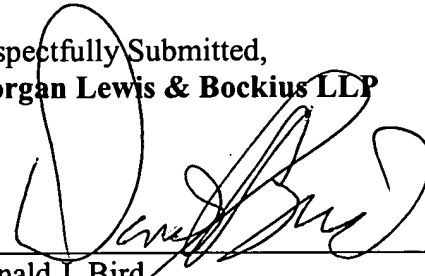
amendment corrects this definition of R<sup>5a</sup> to read “a 4-, 5- or 6-membered saturated heterocyclic group.” However, to make this minor amendment, has been necessary to re-present the entire specification paragraph extending from page 47, line 26 through page 48, line 28, and to repeat this paragraph in the Appendix to show the amendment made. In this regard, the Examiner’s attention is called to the present Appendix at page 15, 5<sup>th</sup> line from the bottom, where the only specification change is shown by **bold underlined text**.

- Similarly, in claim 39 as presented in the Preliminary Amendment of May 6, 2002, the definition of R<sup>5a</sup> was erroneously presented as “a 4- or 6-membered saturated heterocyclic group . . .” See Preliminary Amendment at page 48, line 14-15. This is corrected by the present amendment to read “a 4-, 5- or 6-membered saturated heterocyclic group.” In this regard, the Examiner’s attention is called to the present Appendix at page 24, line 4, where the only change to claim 39 is shown by **bold underlined text**.

***Conclusion***

For the above reasons, and as explained in the Preliminary Amendment, no new matter is introduced by the above amendments. In that they simply correct an inadvertant error in the Preliminary Amendment, entry thereof is believed to be in order and is respectfully requested.

Respectfully Submitted,  
**Morgan Lewis & Bockius LLP**



By: \_\_\_\_\_

Donald J. Bird  
Registration No. 25,323  
Tel. No.: (202) 739-5320  
Fax No.: (202) 739-3001

Date: June 5, 2002  
Morgan Lewis & Bockius LLP  
Customer No. **009629**  
1111 Pennsylvania Avenue, N.W.  
Washington, D.C. 20004  
Tel. No.: 202-739-3000  
DJB:dj

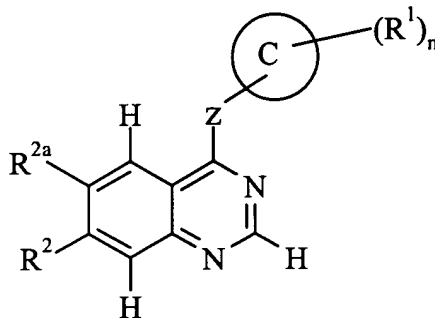
**APPENDIX**  
**VERSION WITH MARKINGS TO SHOW CHANGES**

**IN THE SPECIFICATION:**

The specification has been amended as shown below, wherein additions are indicated by text in **bold underline**, and deletions are indicated by text **[in bold between brackets]**:

The paragraph extending from page 47, line 26 to page 48, line 28 has been amended as follows:

In another aspect of the present invention there is provided the use of compounds of the formula Ia:



(Ia)

[wherein:

ring C,  $R^1$ ,  $R^2$ , n and Z are as defined hereinbefore with the provisos that  $R^2$  is not hydrogen and that Z is not  $CH_2$  or a direct bond; and

$R^{2a}$  represents hydrogen, halogeno,  $C_{1-3}$ alkyl, trifluoromethyl,  $C_{1-3}$ alkoxy,  $C_{1-3}$ alkylsulphanyl,  $-NR^{3a}R^{4a}$  (wherein  $R^{3a}$  and  $R^{4a}$ , which may be the same or different, each represents hydrogen or  $C_{1-3}$ alkyl), or  $R^{5a}(CH_2)_{za}X^{1a}$  (wherein  $R^{5a}$  is a 4-, ~~5~~ or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano,  $C_{1-4}$ cyanoalkyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ hydroxyalkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $C_{1-4}$ alkylsulphonyl $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxycarbonyl,  $C_{1-4}$ aminoalkyl,  $C_{1-4}$ alkylamino, di( $C_{1-4}$

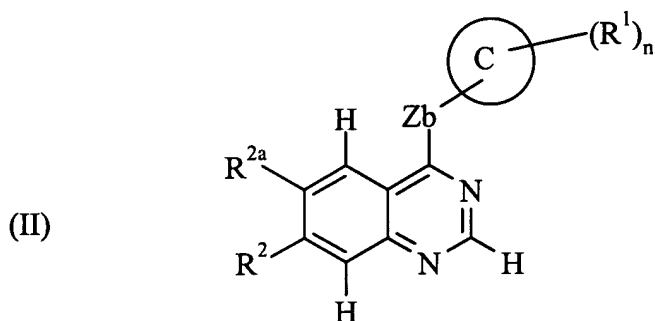
$_4$ alkyl)amino,  $C_{1-4}$ alkylamino $C_{1-4}$ alkyl, di( $C_{1-4}$ alkyl)amino $C_{1-4}$ alkyl,  $C_{1-4}$ alkylamino $C_{1-4}$ alkoxy, di( $C_{1-4}$ alkyl)amino $C_{1-4}$ alkoxy and a group  $-(O-)_f(C_{1-4}alkyl)_g ringD$  (wherein  $f$  is 0 or 1,  $g$  is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from  $C_{1-4}$ alkyl),  $z_a$  is an integer from 0 to 4 and  $X^{1a}$  represents a direct bond,  $-O-$ ,  $-CH_2-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-NR^{6a}C(O)-$ ,  $-C(O)NR^{7a}-$ ,  $-SO_2NR^{8a}-$ ,  $-NR^{9a}SO_2-$  or  $-NR^{10a}-$  (wherein  $R^{6a}$ ,  $R^{7a}$ ,  $R^{8a}$ ,  $R^{9a}$  and  $R^{10a}$  each independently represents hydrogen,  $C_{1-3}$ alkyl or  $C_{1-3}$ alkoxy $C_{2-3}$ alkyl));

and salts thereof, and prodrugs thereof for example esters and amides, in the manufacture of a medicament for use in the production of an antiangiogenic and/or vascular permeability reducing effect in warm-blooded animals such as humans.

### IN THE CLAIMS:

Claim 39 has been amended as follows:

39. (Amended) A compound of the formula II:



wherein:

ring C is an 8, 9, 10, 12 or 13-membered bicyclic or tricyclic moiety which moiety may be saturated or unsaturated, which may be aromatic or non-aromatic, and which optionally may contain 1-3 heteroatoms selected independently from O, N and S;

Zb is  $-O-$  or  $-S-$ ;

$n$  is an integer from 0 to 5;

$R^2$  represents hydrogen, hydroxy, halogeno, cyano, nitro, trifluoromethyl,  $C_{1-3}$ alkyl,  $C_{1-3}$ alkoxy,  $C_{1-3}$ alkylsulphanyl,  $-NR^3R^4$  (wherein  $R^3$  and  $R^4$ , which may be the same or different, each represents hydrogen or  $C_{1-3}$ alkyl),

or  $R^2$  represents a group  $R^5X^1-$ , wherein  $X^1$  represents a direct bond,  $-O-$ ,  $-CH_2-$ ,  $-OC(O)-$ ,  $-C(O)-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-NR^6C(O)-$ ,  $-C(O)NR^7-$ ,  $-SO_2NR^8-$ ,  $-NR^9SO_2-$  or  $-NR^{10}-$  (wherein  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^9$  and  $R^{10}$  each independently represents hydrogen,  $C_{1-3}$ alkyl or  $C_{1-3}$ alkoxy $C_{2-3}$ alkyl), and  $R^5$  is selected from one of the following twenty-two groups:

- 1) hydrogen, oxiranyl $C_{1-4}$ alkyl or  $C_{1-5}$ alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
- 2)  $C_{1-5}$ alkyl $X^2C(O)R^{11}$  (wherein  $X^2$  represents  $-O-$  or  $-NR^{12}-$  (in which  $R^{12}$  represents hydrogen,  $C_{1-3}$ alkyl or  $C_{1-3}$ alkoxy $C_{2-3}$ alkyl) and  $R^{11}$  represents  $C_{1-3}$ alkyl,  $-NR^{13}R^{14}$  or  $-OR^{15}$  (wherein  $R^{13}$ ,  $R^{14}$  and  $R^{15}$  which may be the same or different each represents hydrogen,  $C_{1-5}$ alkyl or  $C_{1-3}$ alkoxy $C_{2-3}$ alkyl));
- 3)  $C_{1-5}$ alkyl $X^3R^{16}$  (wherein  $X^3$  represents  $-O-$ ,  $-S-$ ,  $-SO-$ ,  $-SO_2-$ ,  $-OC(O)-$ ,  $-NR^{17}C(O)-$ ,  $-C(O)NR^{18}-$ ,  $-SO_2NR^{19}-$ ,  $-NR^{20}SO_2-$  or  $-NR^{21}-$  (wherein  $R^{17}$ ,  $R^{18}$ ,  $R^{19}$ ,  $R^{20}$  and  $R^{21}$  each independently represents hydrogen,  $C_{1-3}$ alkyl or  $C_{1-3}$ alkoxy $C_{2-3}$ alkyl) and  $R^{16}$  represents hydrogen,  $C_{1-3}$ alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which  $C_{1-3}$ alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and  $C_{1-4}$ alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano,  $C_{1-4}$ cyanoalkyl,  $C_{1-4}$ alkyl,  $C_{1-4}$ hydroxyalkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $C_{1-4}$ alkylsulphonyl $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxycarbonyl,  $C_{1-4}$ aminoalkyl,  $C_{1-4}$ alkylamino, di( $C_{1-4}$ alkyl)amino,  $C_{1-4}$ alkylamino $C_{1-4}$ alkyl, di( $C_{1-4}$ alkyl)amino $C_{1-4}$ alkyl,  $C_{1-4}$ alkylamino $C_{1-4}$ alkoxy, di( $C_{1-4}$ alkyl)amino $C_{1-4}$ alkoxy and a group  $-(O-)_f(C_{1-4}alkyl)_g$ ringD (wherein  $f$  is 0 or 1,  $g$  is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from  $C_{1-4}$ alkyl));

- 4)  $C_{1-5}alkylX^4C_{1-5}alkylX^5R^{22}$  (wherein  $X^4$  and  $X^5$  which may be the same or different are each -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>23</sup>C(O)-, -C(O)NR<sup>24</sup>-, -SO<sub>2</sub>NR<sup>25</sup>-, -NR<sup>26</sup>SO<sub>2</sub>- or -NR<sup>27</sup>- (wherein R<sup>23</sup>, R<sup>24</sup>, R<sup>25</sup>, R<sup>26</sup> and R<sup>27</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>22</sup> represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl);
- 5) R<sup>28</sup> (wherein R<sup>28</sup> is a 4-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanoalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy and a group  $-(O-)_f(C_{1-4}alkyl)_gringD$  (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl));
- 6)  $C_{1-5}alkylR^{28}$  (wherein R<sup>28</sup> is as defined herein);
- 7)  $C_{2-5}alkenylR^{28}$  (wherein R<sup>28</sup> is as defined herein);
- 8)  $C_{2-5}alkynylR^{28}$  (wherein R<sup>28</sup> is as defined herein);
- 9) R<sup>29</sup> (wherein R<sup>29</sup> represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR<sup>30</sup>R<sup>31</sup>, -NR<sup>32</sup>C(O)R<sup>33</sup> (wherein R<sup>30</sup>, R<sup>31</sup>, R<sup>32</sup> and R<sup>33</sup>, which may be the same or different, each represents hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and a group  $-(O-)_f(C_{1-4}alkyl)_gringD$  (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl));
- 10)  $C_{1-5}alkylR^{29}$  (wherein R<sup>29</sup> is as defined herein);
- 11)  $C_{2-5}alkenylR^{29}$  (wherein R<sup>29</sup> is as defined herein);

- 12) C<sub>2-5</sub>alkynylR<sup>29</sup> (wherein R<sup>29</sup> is as defined herein);
- 13) C<sub>1-5</sub>alkylX<sup>6</sup>R<sup>29</sup> (wherein X<sup>6</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>34</sup>C(O)-, -C(O)NR<sup>35</sup>-, -SO<sub>2</sub>NR<sup>36</sup>-, -NR<sup>37</sup>SO<sub>2</sub>- or -NR<sup>38</sup>- (wherein R<sup>34</sup>, R<sup>35</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>29</sup> is as defined herein);
- 14) C<sub>2-5</sub>alkenylX<sup>7</sup>R<sup>29</sup> (wherein X<sup>7</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>39</sup>C(O)-, -C(O)NR<sup>40</sup>-, -SO<sub>2</sub>NR<sup>41</sup>-, -NR<sup>42</sup>SO<sub>2</sub>- or -NR<sup>43</sup>- (wherein R<sup>39</sup>, R<sup>40</sup>, R<sup>41</sup>, R<sup>42</sup> and R<sup>43</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>29</sup> is as defined herein);
- 15) C<sub>2-5</sub>alkynylX<sup>8</sup>R<sup>29</sup> (wherein X<sup>8</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>44</sup>C(O)-, -C(O)NR<sup>45</sup>-, -SO<sub>2</sub>NR<sup>46</sup>-, -NR<sup>47</sup>SO<sub>2</sub>- or -NR<sup>48</sup>- (wherein R<sup>44</sup>, R<sup>45</sup>, R<sup>46</sup>, R<sup>47</sup> and R<sup>48</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>29</sup> is as defined herein);
- 16) C<sub>1-4</sub>alkylX<sup>9</sup>C<sub>1-4</sub>alkylR<sup>29</sup> (wherein X<sup>9</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>49</sup>C(O)-, -C(O)NR<sup>50</sup>-, -SO<sub>2</sub>NR<sup>51</sup>-, -NR<sup>52</sup>SO<sub>2</sub>- or -NR<sup>53</sup>- (wherein R<sup>49</sup>, R<sup>50</sup>, R<sup>51</sup>, R<sup>52</sup> and R<sup>53</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>29</sup> is as defined herein);
- 17) C<sub>1-4</sub>alkylX<sup>9</sup>C<sub>1-4</sub>alkylR<sup>28</sup> (wherein X<sup>9</sup> and R<sup>28</sup> are as defined herein);
- 18) C<sub>2-5</sub>alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C<sub>1-4</sub>alkylamino, N,N-di(C<sub>1-4</sub>alkyl)amino, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl and N,N-di(C<sub>1-4</sub>alkyl)aminosulphonyl;
- 19) C<sub>2-5</sub>alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C<sub>1-4</sub>alkylamino, N,N-di(C<sub>1-4</sub>alkyl)amino, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl and N,N-di(C<sub>1-4</sub>alkyl)aminosulphonyl;
- 20) C<sub>2-5</sub>alkenylX<sup>9</sup>C<sub>1-4</sub>alkylR<sup>28</sup> (wherein X<sup>9</sup> and R<sup>28</sup> are as defined herein);
- 21) C<sub>2-5</sub>alkynylX<sup>9</sup>C<sub>1-4</sub>alkylR<sup>28</sup> (wherein X<sup>9</sup> and R<sup>28</sup> are as defined herein); and
- 22) C<sub>1-4</sub>alkylR<sup>54</sup>(C<sub>1-4</sub>alkyl)<sub>q</sub>(X<sup>9</sup>)<sub>r</sub>R<sup>55</sup> (wherein X<sup>9</sup> is as defined herein, q is 0 or 1, r is 0 or 1, and R<sup>54</sup> and R<sup>55</sup> are each independently selected from hydrogen, C<sub>1-3</sub>alkyl, cyclopentyl, cyclohexyl and a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C<sub>1-3</sub>alkyl group may bear



1 or 2 substituents selected from oxo, hydroxy, halogeno and C<sub>1-4</sub>alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanoalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy and a group  $-(O-)_f(C_{1-4}alkyl)_g ringD$  (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl), with the proviso that R<sup>54</sup> cannot be hydrogen);

and additionally wherein any C<sub>1-5</sub>alkyl, C<sub>2-5</sub>alkenyl or C<sub>2-5</sub>alkynyl group in R<sup>5</sup>X<sup>1</sup> - may bear one or more substituents selected from hydroxy, halogeno and amino;

R<sup>1</sup> represents hydrogen, oxo, halogeno, hydroxy, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxymethyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>haloalkyl, cyano, amino, C<sub>2-5</sub>alkenyl, C<sub>2-5</sub>alkynyl, C<sub>1-3</sub>alkanoyloxy, nitro, C<sub>1-4</sub>alkanoylamino, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>alkylsulphanyl, C<sub>1-4</sub>alkylsulphinyl, C<sub>1-4</sub>alkylsulphonyl, carbamoyl, N-C<sub>1-4</sub>alkylcarbamoyl, N,N-di(C<sub>1-4</sub>alkyl)carbamoyl, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl, N,N-di(C<sub>1-4</sub>alkyl)aminosulphonyl, N-(C<sub>1-4</sub>alkylsulphonyl)amino, N-(C<sub>1-4</sub>alkylsulphonyl)-N-(C<sub>1-4</sub>alkyl)amino, N,N-di(C<sub>1-4</sub>alkylsulphonyl)amino, a C<sub>3-7</sub>alkylene chain joined to two ring C carbon atoms, C<sub>1-4</sub>alkanoylaminoC<sub>1-4</sub>alkyl, carboxy,

or R<sup>1</sup> represents a group R<sup>56</sup>X<sup>10</sup>, wherein X<sup>10</sup> represents a direct bond, -O-, -CH<sub>2</sub>-, -OC(O)-, -C(O)-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>57</sup>C(O)-, -C(O)NR<sup>58</sup>-, -SO<sub>2</sub>NR<sup>59</sup>-, -NR<sup>60</sup>SO<sub>2</sub>- or -NR<sup>61</sup>- (wherein R<sup>57</sup>, R<sup>58</sup>, R<sup>59</sup>, R<sup>60</sup> and R<sup>61</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl), and R<sup>56</sup> is selected from one of the following twenty-two groups:

- 1) hydrogen, oxiranylC<sub>1-4</sub>alkyl or C<sub>1-5</sub>alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, chloro, bromo and amino;
- 2) C<sub>1-5</sub>alkylX<sup>11</sup>C(O)R<sup>62</sup> (wherein X<sup>11</sup> represents -O- or -NR<sup>63</sup>- (in which R<sup>63</sup> represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>62</sup> represents C<sub>1-3</sub>alkyl, -NR<sup>64</sup>R<sup>65</sup> or

- OR<sup>66</sup> (wherein R<sup>64</sup>, R<sup>65</sup> and R<sup>66</sup> which may be the same or different each represents hydrogen, C<sub>1-5</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl));
- 3) C<sub>1-5</sub>alkylX<sup>12</sup>R<sup>67</sup> (wherein X<sup>12</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -OC(O)-, -NR<sup>68</sup>C(O)-, -C(O)NR<sup>69</sup>-, -SO<sub>2</sub>NR<sup>70</sup>-, -NR<sup>71</sup>SO<sub>2</sub>- or -NR<sup>72</sup>- (wherein R<sup>68</sup>, R<sup>69</sup>, R<sup>70</sup>, R<sup>71</sup> and R<sup>72</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>67</sup> represents hydrogen, C<sub>1-3</sub>alkyl, cyclopentyl, cyclohexyl or a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C<sub>1-3</sub>alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C<sub>1-4</sub>alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanoalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy and a group -(O-)<sub>f</sub>(C<sub>1-4</sub>alkyl)<sub>g</sub>ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl));
- 4) C<sub>1-5</sub>alkylX<sup>13</sup>C<sub>1-5</sub>alkylX<sup>14</sup>R<sup>73</sup> (wherein X<sup>13</sup> and X<sup>14</sup> which may be the same or different are each -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>74</sup>C(O)-, -C(O)NR<sup>75</sup>-, -SO<sub>2</sub>NR<sup>76</sup>-, -NR<sup>77</sup>SO<sub>2</sub>- or -NR<sup>78</sup>- (wherein R<sup>74</sup>, R<sup>75</sup>, R<sup>76</sup>, R<sup>77</sup> and R<sup>78</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>73</sup> represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl);
- 5) R<sup>79</sup> (wherein R<sup>79</sup> is a 4-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanoalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy and a group -(O-)<sub>f</sub>(C<sub>1-4</sub>alkyl)<sub>g</sub>ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered

- saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl));
- 6) C<sub>1-5</sub>alkylR<sup>79</sup> (wherein R<sup>79</sup> is as defined herein);
- 7) C<sub>2-5</sub>alkenylR<sup>79</sup> (wherein R<sup>79</sup> is as defined herein);
- 8) C<sub>2-5</sub>alkynylR<sup>79</sup> (wherein R<sup>79</sup> is as defined herein);
- 9) R<sup>80</sup> (wherein R<sup>80</sup> represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents selected from hydroxy, halogeno, amino, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, C<sub>1-4</sub>hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -C(O)NR<sup>81</sup>R<sup>82</sup>, -NR<sup>83</sup>C(O)R<sup>84</sup> (wherein R<sup>81</sup>, R<sup>82</sup>, R<sup>83</sup> and R<sup>84</sup>, which may be the same or different, each represents hydrogen, C<sub>1-4</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and a group -(O-)<sub>f</sub>(C<sub>1-4</sub>alkyl)<sub>g</sub>ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl));
- 10) C<sub>1-5</sub>alkylR<sup>80</sup> (wherein R<sup>80</sup> is as defined herein);
- 11) C<sub>2-5</sub>alkenylR<sup>80</sup> (wherein R<sup>80</sup> is as defined herein);
- 12) C<sub>2-5</sub>alkynylR<sup>80</sup> (wherein R<sup>80</sup> is as defined herein);
- 13) C<sub>1-5</sub>alkylX<sup>15</sup>R<sup>80</sup> (wherein X<sup>15</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>85</sup>C(O)-, -C(O)NR<sup>86</sup>-, -SO<sub>2</sub>NR<sup>87</sup>-, -NR<sup>88</sup>SO<sub>2</sub>- or -NR<sup>89</sup>- (wherein R<sup>85</sup>, R<sup>86</sup>, R<sup>87</sup>, R<sup>88</sup> and R<sup>89</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>80</sup> is as defined herein);
- 14) C<sub>2-5</sub>alkenylX<sup>16</sup>R<sup>80</sup> (wherein X<sup>16</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>90</sup>C(O)-, -C(O)NR<sup>91</sup>-, -SO<sub>2</sub>NR<sup>92</sup>-, -NR<sup>93</sup>SO<sub>2</sub>- or -NR<sup>94</sup>- (wherein R<sup>90</sup>, R<sup>91</sup>, R<sup>92</sup>, R<sup>93</sup> and R<sup>94</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>80</sup> is as defined herein);
- 15) C<sub>2-5</sub>alkynylX<sup>17</sup>R<sup>80</sup> (wherein X<sup>17</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>95</sup>C(O)-, -C(O)NR<sup>96</sup>-, -SO<sub>2</sub>NR<sup>97</sup>-, -NR<sup>98</sup>SO<sub>2</sub>- or -NR<sup>99</sup>- (wherein R<sup>95</sup>, R<sup>96</sup>, R<sup>97</sup>, R<sup>98</sup> and R<sup>99</sup> each

independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>80</sup> is as defined herein);

- 16) C<sub>1-4</sub>alkylX<sup>18</sup>C<sub>1-4</sub>alkylR<sup>80</sup> (wherein X<sup>18</sup> represents -O-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>100</sup>C(O)-, -C(O)NR<sup>101</sup>-, -SO<sub>2</sub>NR<sup>102</sup>-, -NR<sup>103</sup>SO<sub>2</sub>- or -NR<sup>104</sup>- (wherein R<sup>100</sup>, R<sup>101</sup>, R<sup>102</sup>, R<sup>103</sup> and R<sup>104</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl) and R<sup>80</sup> is as defined herein);
- 17) C<sub>1-4</sub>alkylX<sup>18</sup>C<sub>1-4</sub>alkylR<sup>79</sup> (wherein X<sup>18</sup> and R<sup>79</sup> are as defined herein);
- 18) C<sub>2-5</sub>alkenyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C<sub>1-4</sub>alkylamino, N,N-di(C<sub>1-4</sub>alkyl)amino, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl and N,N-di(C<sub>1-4</sub>alkyl)aminosulphonyl;
- 19) C<sub>2-5</sub>alkynyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro, amino, C<sub>1-4</sub>alkylamino, N,N-di(C<sub>1-4</sub>alkyl)amino, aminosulphonyl, N-C<sub>1-4</sub>alkylaminosulphonyl and N,N-di(C<sub>1-4</sub>alkyl)aminosulphonyl;
- 20) C<sub>2-5</sub>alkenylX<sup>18</sup>C<sub>1-4</sub>alkylR<sup>79</sup> (wherein X<sup>18</sup> and R<sup>79</sup> are as defined herein);
- 21) C<sub>2-5</sub>alkynylX<sup>18</sup>C<sub>1-4</sub>alkylR<sup>79</sup> (wherein X<sup>18</sup> and R<sup>79</sup> are as defined herein); and
- 22) C<sub>1-4</sub>alkylR<sup>105</sup>(C<sub>1-4</sub>alkyl)<sub>x</sub>(X<sup>18</sup>)<sub>y</sub>R<sup>106</sup> (wherein X<sup>18</sup> is as defined herein, x is 0 or 1, y is 0 or 1, and R<sup>105</sup> and R<sup>106</sup> are each independently selected from hydrogen, C<sub>1-3</sub>alkyl, cyclopentyl, cyclohexyl and a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C<sub>1-3</sub>alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C<sub>1-4</sub>alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanoalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy and a group  $-(O-)_f(C_{1-4}alkyl)_g$ ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl) with the proviso that R<sup>105</sup> cannot be hydrogen);

and additionally wherein any C<sub>1-5</sub>alkyl, C<sub>2-5</sub>alkenyl or C<sub>2-5</sub>alkynyl group in R<sup>56</sup>X<sup>10</sup>- may bear one or more substituents selected from hydroxy, halogeno and amino;

R<sup>2a</sup> represents hydrogen, halogeno, C<sub>1-3</sub>alkyl, trifluoromethyl, C<sub>1-3</sub>alkoxy, C<sub>1-3</sub>alkylsulphanyl, -NR<sup>3a</sup>R<sup>4a</sup> (wherein R<sup>3a</sup> and R<sup>4a</sup>, which may be the same or different, each represents hydrogen or C<sub>1-3</sub>alkyl), or R<sup>5a</sup>(CH<sub>2</sub>)<sub>za</sub>X<sup>1a</sup> (wherein R<sup>5a</sup> is a 4-, 5- or 6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, cyano, C<sub>1-4</sub>cyanoalkyl, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>hydroxyalkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylsulphonylC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxycarbonyl, C<sub>1-4</sub>aminoalkyl, C<sub>1-4</sub>alkylamino, di(C<sub>1-4</sub>alkyl)amino, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkyl, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkylaminoC<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminoC<sub>1-4</sub>alkoxy and a group -(O-)<sub>f</sub>(C<sub>1-4</sub>alkyl)<sub>g</sub>ringD (wherein f is 0 or 1, g is 0 or 1 and ring D is a 4-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which cyclic group may bear one or more substituents selected from C<sub>1-4</sub>alkyl), za is an integer from 0 to 4 and X<sup>1a</sup> represents a direct bond, -O-, -CH<sub>2</sub>-, -S-, -SO-, -SO<sub>2</sub>-, -NR<sup>6a</sup>C(O)-, -C(O)NR<sup>7a</sup>-, -SO<sub>2</sub>NR<sup>8a</sup>-, -NR<sup>9a</sup>SO<sub>2</sub>- or -NR<sup>10a</sup>- (wherein R<sup>6a</sup>, R<sup>7a</sup>, R<sup>8a</sup>, R<sup>9a</sup> and R<sup>10a</sup> each independently represents hydrogen, C<sub>1-3</sub>alkyl or C<sub>1-3</sub>alkoxyC<sub>2-3</sub>alkyl));

or a salt or prodrug thereof;

with the proviso that R<sup>2</sup> is not hydrogen, and excluding the compounds:

6,7-dimethoxy-4-(1-naphthylsulphanyl)quinazoline,

6,7-dimethoxy-4-(2-naphthylsulphanyl)quinazoline,

6,7-dimethoxy-4-(1-naphthyloxy)quinazoline and

6,7-dimethoxy-4-(2-naphthyloxy)quinazoline.